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The natural history of childhood food allergy

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INTRODUCTION — Understanding the natural history of food allergy in childhood is essential in managing patients with these disorders. The natural history of a food allergy includes information on the acquisition of the allergy, the likelihood that it will be outgrown, and its usual duration.

Food allergy most often begins in the first two years of life. Certain food allergies, such as those to cow's milk and hen's egg, are usually outgrown during childhood or adolescence, whereas peanut and tree nut allergies are more likely to persist into adulthood.

This topic review provides an overview of the natural history of food allergy in children. The clinical manifestations and treatment of food allergy are discussed separately. (See "[Clinical manifestations of food allergy: An overview](#)".)

DEFINITION OF FOOD ALLERGY — In this section, the terms "allergy" and "hypersensitivity" are used interchangeably to refer to an abnormal immunologic reaction to food. Such reactions can be mediated by IgE molecules directed against specific food proteins that activate mast cells and basophils, or can arise from other cellular processes involving eosinophils or T cells. (See "[Clinical manifestations of food allergy: An overview](#)".)

PREVALENCE OF CHILDHOOD FOOD ALLERGY — Most food allergy is acquired in the first or second year of life. The peak prevalence of food allergy is approximately 6 to 8 percent at one year of age, although rates as high as 10 percent have been reported [1-4]. It then falls progressively until late childhood, after which the prevalence remains stable at about 3 to 4 percent.

Parentally-perceived food allergy is common in early childhood, with up to one-third

of parents reporting one or more adverse food reactions [5-9]. Parentally-reported adverse food reactions were assessed with a prospective study of 3623 children, followed from birth until the age of two [5,6,10]. Parents completed questionnaires at six-month intervals. The cumulative incidence of adverse food reactions was 35 percent by age two. Cow's milk, fruits (especially citrus and strawberry), and vegetables (especially tomato), accounted for nearly two-thirds of all reported reactions. Cow's milk was the single food item most commonly incriminated, with a cumulative incidence of 12 percent. Other problematic foods reported by parents included egg (4.4 percent), fish (3 percent), nuts (2.1 percent), and cereals (1.4 percent). The overall duration of food reactivity was short, with approximately two-thirds of the reactions resolving within six months of their onset. The probable explanation for the brief duration of most of these reactions is the commonplace nature of irritant, non-immunologic food reactions in infants and young children. Mild perioral rashes after eating tomatoes or berries are examples, although IgE-mediated allergies to these foods are also possible.

Variable criteria are used to measure food allergy. In studying IgE-mediated allergy, some researchers examine rates of "sensitization," or the presence of IgE directed against a specific food, as detected by in vivo (skin testing) or in vitro testing for specific IgE (often called radioallergosorbent testing, or RAST, though nowadays the test uses fluorescence rather than radioactivity, and is termed FEIA for fluorescent-enzyme immunoassay). This is distinct from clinical reactivity, which is the development of symptoms on exposure to a food, as assessed by history or challenge. This distinction occurs because not all patients with detectable food-specific IgE antibodies will have a reaction when the food is ingested. Less commonly, patients may have clear histories of food allergic reactions with low or undetectable levels of food-specific IgE. Thus, studies measuring sensitization to food allergens may overestimate the prevalence of true food allergy.

The German Multicenter Allergy Study followed the development of sensitization to common food allergens in a large cohort of children, without clinical confirmation of food reactions [11-13]. A total of 216 children from a birth cohort of 4082 children were assessed with serum food-specific IgE testing approximately yearly. The overall annual incidence rates for food sensitization decreased from a peak of 10 percent at age one, to 3 percent at age six. Sensitization to hen's egg and cow's milk were most common, with peak prevalence rates of about 6 percent at age one, followed by wheat and soy.

In contrast, the rates of food allergy are significantly lower if allergy is defined by verified clinical reactivity upon ingestion. As an example, a cohort of 1749 children was followed from birth to determine the prevalence of cow's milk allergy during the first year of life [14]. The children were evaluated by history, milk elimination, oral challenge, and skin prick tests or serum food-specific IgE testing. A confirmed

reactivity rate of 2.2 percent was reported.

An association between early food allergy and later atopic respiratory conditions has been noted in multiple studies [11,14-16]. A child with food allergy has between a 50 and 90 percent chance of subsequently developing asthma. Young children who are sensitized to food in infancy, particularly egg, often develop subsequent sensitization to aeroallergens. In one study, a serum RAST result for egg >2 kUA/L at age 12 months was 99 percent specific and had a 77 percent positive predictive value for sensitization to respiratory allergens by three years, even in the absence of other risk factors, such as family history of atopy [11].

In summary, more than one-third of parents will report adverse food reactions in their young children, although the rates of verifiable food allergy are much lower. Food sensitization and/or allergy are present in 5 to 10 percent of young children with peak prevalence at about one year of age. Studies that measure sensitization to food allergens can overestimate the prevalence of true allergic reactions to foods, because not all sensitized children will develop symptoms upon ingestion. Young children who are sensitized to foods or have confirmed IgE-mediated food allergy are more likely than their non-allergic peers to develop allergic rhinitis and asthma later on.

OVERVIEW OF RESOLUTION — The majority of childhood food allergies are lost over time, although the process of resolution varies a great deal among different foods and individual patients.

Patterns — Food allergies to most foods, other than fish/shellfish and peanut/tree nuts, are usually outgrown:

- In one study, 82 children aged 6 months to 14 years with a variety of food allergies were followed for a period of two to five years [17]. Of the 12 children who were allergic to cow's milk, four developed complete tolerance, seven had reduced sensitivity, and only one remained unchanged by the completion of the study. Of 55 children with egg allergy, 20 developed complete tolerance, 24 had reduced sensitivity, and 11 remained unchanged. These results are very different from those for fish and peanut/tree nut allergy. Of 32 patients with fish allergy, only five developed tolerance and none of the 35 children with peanut/tree nut allergy developed tolerance.
- In a similar study of 75 patients (between the ages of 3 and 18 years) with atopic dermatitis and food allergy, patients underwent yearly rechallenge with each of the foods that had previously elicited a positive reaction [18]. Diagnoses of food allergy were made by skin testing, RASTs, and/or double-blind, placebo-controlled food challenges (DBPCFC). After one to two years of follow-up, soy, wheat, egg, peanut, and cow's milk allergy had been lost in

50, 33, 24, 20, and 19 percent, respectively.

These studies were not large enough to discern whether there were differences in the natural histories of children diagnosed in very early life compared to those diagnosed in later childhood.

Mechanisms — The mechanisms by which food allergy resolves are not fully understood, and it is likely that multiple mechanisms are involved. Food-specific IgE levels tend to fall over time in most patients with food allergy, and this loss of IgE is the best known predictor of the development of clinical tolerance. However, it is also clear that some patients become tolerant even with persistently elevated food-specific IgE levels, and thus, loss of IgE is not a requirement for, or even the primary mechanism of the resolution of food allergy in these patients. Other humoral changes, including increased levels of allergen-specific IgG4 and/or mucosal IgA, may also play a role. Alternately, cellular changes, such as the induction of T regulatory cells, may be important.

Role of avoidance — Strict dietary avoidance of the foods to which a child is allergic has been a mainstay of food allergy management, based upon the clinical impression that avoidance increases the chance of outgrowing an allergy and may hasten resolution. However, few studies address this issue [19,20]. In one study of children with egg allergy, neither strict avoidance nor accidental exposure, assessed by recall questionnaire, impacted the development of tolerance [21].

Clinician-supervised oral food challenges are often required to determine if an allergy has resolved. Clinical experience suggests that food challenges that result in an allergic reaction do not alter the natural course of resolution of food allergy, although studies have not specifically addressed this issue.

Studies of oral food challenges reveal that individuals vary with regard to the threshold amount of food that triggers a reaction [22]. However, strict avoidance is generally advised, rather than having patients ingest an allergen in subthreshold amounts, because patients may accidentally consume a larger amount than intended and elicit an allergic reaction.

Some children who react to whole egg (eg, scrambled) or dairy (eg, liquid milk, yogurt) can tolerate extensively heated forms of these allergens in smaller quantities in foods, such as baked muffins [23,24]. Whether allowing this "less strict" avoidance alters the natural course of allergy remains unknown [25,26]. (See "[Food allergen avoidance](#)", section on 'How strict must avoidance be?'.)

Some patients demonstrate sensitization to a food that they consume (eg, a positive allergen prick skin test or elevated specific serum IgE), but they do not have a clear history of reactions to that food. Several small case series have reported that invoking strict avoidance of the food occasionally results in acute and

severe reactions to the self-same food upon reintroduction [[27-29](#)]. This phenomenon may represent a loss of a desensitized state to a food that was maintained while it was being regularly ingested. However, there are no formal studies assessing the risk of occurrence of this uncommon outcome, and removal of foods from the diet is often required to diagnose and treat chronic allergic conditions.

In practice, some children rapidly outgrow their food allergies without strict avoidance and others, despite the most stringent diet, do not. Because strict avoidance is so difficult, it would be helpful to understand the impact of continued exposure on the natural history of food allergy. Until we do, however, it is still likely that the majority of children with food allergy will benefit from strict avoidance, at least to avoid provoking symptoms.

MONITORING THE FOOD-ALLERGIC CHILD — The food allergic child must be followed regularly by both the pediatrician and allergist to assure that growth and development are normal. The allergist should review all accidental exposures and food reactions in order to assure that avoidance measures are adequate, reactions are recognized promptly and treated appropriately, epinephrine autoinjectors are current and available to the child in all settings (if appropriate), and that the patient and caregivers understand the management plan.

Serial testing — The allergist should evaluate the child at regular intervals to determine if the allergy has been outgrown. This is usually done yearly; however, longer or shorter intervals may be more appropriate in some situations. As examples, a child with a reaction to fruit might be evaluated every six months, and an older child with persistent peanut allergy may not need annual testing after the first few years if there is no indication of improvement.

Reevaluation can be accomplished with in vitro testing, skin prick testing, and information on accidental exposures. The optimal method of monitoring specific food allergies has not yet been determined, and various approaches can be used. We use the clinical history and in vitro testing (CAP-FEIA) to follow patients in our clinic. We generally do not perform repeat skin testing, as we feel it does not change our management in the majority of cases. However, other centers do use skin testing, especially in making decisions about whether or not to proceed to an oral challenge.

In vitro testing for allergic disease is reviewed separately. (See "[Overview of in vitro allergy tests](#)".)

Determining if an allergy has resolved — Supervised food challenge is recommended to prove the condition has been outgrown, because negative tests do not guarantee loss of allergy with absolute certainty, and positive tests can persist

even after an allergy has resolved [30,31]. These must be performed with caution and with full emergency equipment and medications on hand to treat possible reactions. (See "[Oral food challenges for diagnosis and management of food allergies](#)".)

If there is no interim history to suggest a recent reaction, then we recommend the following reevaluation for children with specific childhood food allergies:

Cow's milk and egg — IgE-mediated allergies to milk and egg are usually lost gradually throughout childhood and adolescence. We retest yearly with CAP-FEIA testing. The rate of decline can predict the likelihood that a challenge will be negative. We usually offer challenge to milk and egg when the specific IgE level is ≤ 2 kUA/L, which gives the patient an approximately 50 percent chance of passing the challenge in our patient population. However, positive predictive values for both specific IgE and skin prick testing may vary depending on the population studied [32]. Lower cutoffs may be used for children under two years of age. (See '[Cow's milk](#)' below and '[Hen's egg](#)' below.)

Non-IgE-mediated CMA tends to be outgrown more quickly and a careful challenge is warranted by the age of two to three years if there have been no recent reactions from accidental exposures. Reintroduction of food in dietary or food-protein induced enterocolitis syndrome (FPIES), in particular, is associated with significant risk. Challenges in patients with FPIES who were very ill upon presentation should be performed under close supervision in a hospital setting. This is reviewed in more detail elsewhere. (See "[Food protein-induced proctitis/colitis, enteropathy, and enterocolitis of infancy](#)".)

Peanut or tree nut — We recommend repeat testing yearly with CAP-FEIA testing. Patients with TN- or PN-IgE level ≤ 2 kUA/L should be offered a supervised challenge. If negative, the patient should be advised to ingest nut at least once a week. The optimal amount of nut that patients should eat monthly is unknown. We therefore suggest that they ingest a serving (eg, the amount in a peanut butter sandwich or nut-containing candy bar). Patients should be followed for at least another year to assure that there are no recurrent symptoms.

In patients with persistent allergy, or if the CAP-FEIA remains unchanged for several years, testing can be performed less frequently over time.

Wheat — A wheat-specific IgE level predictive of clinical reactivity has not been determined, due to poor performance characteristics of the IgE assay for this allergen [33]. Proposed challenge decision points range from 20 to 100 kU/L [31,34]. In one survey, 60 percent of patients with a wheat IgE level < 20 kU/L passed their challenges and 50 percent of those with a wheat IgE level of < 50 kU/L passed [35]. Peak wheat-specific IgE has some predictive value in determining the

age at which tolerance develops and higher levels may indicate risk of persistent allergy [35]. (See '[Wheat allergy](#)' below.)

We suggest that patients with wheat allergy or sensitization undergo serial oral challenges to wheat at least every two years, in the absence of an interval history of symptoms triggered by an exposure. Additional variables to take into consideration before proceeding with the challenge include the wheat-specific IgE level and how it compares to the level at the time of the last challenge, the result of the last challenge (eg, did the reaction occur at the beginning or near the end of the challenge and what was the severity of the reaction?), and the age of the child (eg, resolution may occur at later ages, but is more likely to occur in a two-year time span in a younger child).

Soy — We recommend repeat evaluation yearly with CAP-FEIA testing. These allergies are generally outgrown more quickly than those to egg or milk. Challenge can be offered when the results of in vitro testing have reached low levels, although these are not as well defined as for the previous foods, and the situation is probably similar to that for wheat.

Other foods — Yearly in vitro testing is our general recommendation. As mentioned previously, repeat evaluation can be less frequent with time if there is minimal evidence of improvement over several years.

NATURAL HISTORY OF SPECIFIC ALLERGIES — Issues relating to prevalence, resolution, and recurrences of food allergy are best understood with respect to the specific food. The most reliable information concerns allergies to cow's milk, hen's egg, peanut/tree nuts, and wheat. The natural history of other food allergies, such as allergies to soy and sesame, has been less well studied.

Cow's milk — Cow's milk allergy (CMA) is the most common food allergy among infants and young children. Resolution is gradual throughout childhood and adolescence, and is influenced by various factors.

Up to 50 percent of children with CMA also have concomitant adverse reactions to other foods [36]. In addition, 50 to 80 percent have allergic rhinitis and asthma in response to inhaled environmental allergens by puberty.

Prevalence — CMA affects approximately 2.5 percent of children during the first two years of life [6,14,36]. One of the best studies of CMA prevalence is the large prospective Danish study reviewed previously [14]. Cow's milk allergy was confirmed in 2.2 percent of children followed from birth through age three years. Of note, nearly one-half of these cases were non-IgE-mediated allergic conditions, such as dietary protein-induced proctitis/colitis, enteropathy, and enterocolitis. The estimated overall prevalence in the United States in a national survey was 0.4 percent, based upon serologic testing [3]. (See '[Food protein-induced](#)

proctitis/colitis, enteropathy, and enterocolitis of infancy".)

Resolution — The resolution of CMA is variable, depending upon the type of allergy (IgE-mediated or non-IgE-mediated) [[14,30,36](#)] and the population examined (general public or referral populations) [[14,24](#)]. Concomitant allergic rhinitis and asthma may also be risk factors for persistent food allergies.

Resolution rates for IgE-mediated CMA are significantly lower than those of non-IgE-mediated milk allergy:

- One study followed 98 children (median age 24 months) with CMA for a median of two years (range: 6 to 72 months) [[30](#)]. Twenty-two percent of those with IgE-mediated allergy (representing approximately two-thirds of the total group) became tolerant, whereas 59 percent of those with non-IgE-mediated CMA became tolerant.
- Another study followed 139 children with CMA (aged 14 months to 18 years at the end of the study) for an average of seven years [[37](#)]. Sixty-six of the children had IgE-mediated CMA. In the whole group, CMA resolved in 34 percent by age two years, 55 percent by age five, and 68 percent by age 10. However, tolerance was delayed in the subgroup of children with IgE-mediated CMA, with resolution occurring in none of these children by age two years, 22 percent by age five, and 43 percent by age 10.
- In the Danish study previously described, 76 percent of those with IgE-mediated allergy had become cow's milk tolerant, and 100 percent of those with non-IgE-mediated allergy were tolerant by age three years [[14](#)]. Of note, these rates of resolution were much higher than those in subsequent studies, and may be due to the recruitment of affected children from the general population, in whom the range of disease severity is likely to be broad.

Resolution rates vary in different study populations:

- Rates of resolution in children with IgE-mediated CMA followed in allergy practices are lower than those of children in the general population, probably because these children are more severely allergic, although other confounders have not been excluded. One large retrospective study reported resolution rates in 807 children with CMA who were followed by allergy specialists [[24](#)]. If resolution was defined as passing a challenge procedure or having a cow's milk-specific IgE (CM-IgE) of <3 kUA/L and no reactions within the past year, CMA resolved in 19, 42, 64, and 79 percent of children at ages 4, 8, 12, and 16 years, respectively.

Finally, the presence of concomitant allergic rhinitis or asthma is associated with the persistence of IgE-mediated CMA [24,38]. As an example, an Israeli study followed 105 children with cow's milk allergy for a period of eight years [38]. Sixty-one percent of patients with persistent CMA had asthma, compared to 19 percent in the resolution group. However, this association may just reflect the fact that these children were followed later into childhood than children whose allergy had resolved.

Milk-specific IgE — In general, the higher the CM-IgE, the less likely the child is to become tolerant over time. In the retrospective study discussed previously, persistence was more likely in patients with higher initial levels of CM-IgE. Median CM-IgE in the first two years of life was 19 kUA/L in the children with CMA that persisted, compared to 1.8 kUA/L in those with CMA that eventually resolved [24]. In addition, CM-IgE levels in persistent CMA tended to increase over the first three to four years of life and then gradually decrease, while those in resolving CMA were stable initially and then gradually declined ([figure 1](#)).

Another study examined the rate of change in levels of CM-IgE over time, in relation to the patient's age, in children who developed CMA before the age of four years [39]. CM-IgE levels decreased more rapidly in those who developed tolerance. Independent of initial levels, the percentage amount that CM-IgE dropped in one year correlated with the likelihood that the child would pass a food challenge performed at that time. If the CM-IgE dropped 50, 75, 90, and 99 percent, there was a 31, 45, 66, and 95 percent chance of passing challenge, respectively.

IgE molecules are not equally pathogenic, and IgE directed against certain types of epitopes may be associated with persistent allergy [40-42]. However, the food-specific IgE tests that are currently available commercially do not distinguish among IgE molecules directed toward different epitopes.

- IgE- and IgG-binding epitopes on alpha-s1-casein (a significant milk allergen) were identified using the sera of 24 cow's milk-allergic children [40]. Epitope recognition patterns in older children with persistent milk allergy were compared to those in younger children who were likely to outgrow their allergy. Although there were no differences in binding of IgG between the two groups, two IgE-binding regions were recognized by the majority of the older children with persistent allergy, but none of the younger children.
- A similar analysis was performed in subsequent studies of IgE- and IgG-binding epitopes on beta- and kappa-casein in cow's milk-allergic patients [41,43]. Three IgE-binding regions on beta-casein and six on kappa-casein were recognized by patients with persistent cow's milk allergy, but not by

those with transient allergy.

- A third study found that patients with persistent cow's milk allergy had higher levels of IgE to linear (primary sequence) epitopes (rather than tertiary or conformational epitopes) from alpha-s1-casein and beta-casein than children who achieved tolerance [42].

Such data may lead to new clinical tests, such as epitope-specific RASTs, that will permit the identification of children who are at risk for persistent cow's milk allergy.

Summary — CMA affects 2 to 3 percent of children during the first two years of life. Observations concerning CMA resolution include the following:

- Non-IgE-mediated CMA appears to be a transient childhood condition, which is almost always outgrown. By comparison, IgE-mediated CMA may persist through adolescence and beyond.
- In counseling patients and families, the pediatrician treating the general population can expect high rates of resolution, whereas allergy specialists with referred patient populations should anticipate lower resolution rates.
- Children with IgE-mediated CMA and higher peak CM-IgE levels tend to have more persistent disease.
- Children with allergic rhinitis or asthma are more likely to have IgE-mediated CMA that persists.

Hen's egg — Hen's egg allergy is one of the most common food allergies of childhood, and like cow's milk allergy, it is frequently outgrown during childhood or adolescence. The presence of egg allergy is a marker for subsequent sensitization to aeroallergens, as well as the later development of asthma [11,44].

Prevalence — Egg allergy affects 1 to 2 percent of young children [2,10]. The estimated overall prevalence in the United States in a national survey was 0.2 percent, based upon serologic testing [3]. Most reactions are IgE-mediated.

Resolution — Allergy to egg usually resolves within several years of diagnosis [17,39,45,46].

- The rate of resolution of egg allergy was estimated in one prospective study that followed 58 children, beginning at ages younger than two years [46]. One-half of children became tolerant by 35 months of follow-up (4 to 4.5 years old), and two-thirds became tolerant by five years of follow-up.
- A retrospective study of 881 children with egg allergy followed by allergy specialists found that resolution was slower in this referral population [23].

When resolution was defined as passing a challenge procedure involving the ingestion of one whole cooked egg, egg allergy resolved in 4, 26, 48, and 68 percent of children at ages 4, 8, 12, and 16 years, respectively. An egg-specific IgE (E-IgE) level ≥ 50 kUA/L was a marker of persistent egg allergy in this study population.

- Tolerance to egg in baked goods is common and typically occurs at an earlier age than tolerance to lightly cooked or raw egg [[23,47-49](#)]. In one series of children with egg allergy, the median age of tolerance to well-cooked egg was 5.6 years versus a median of 10.3 years for uncooked egg [[49](#)].
- Egg-specific IgE levels decreased more rapidly in those children who developed tolerance than in those with persistent allergy, as with cow's milk allergy [[39](#)]. In a group of children who developed food allergy before the age of four, the percentage amount that E-IgE dropped in one year correlated with the likelihood that the child would pass a food challenge performed at that time. If the E-IgE dropped 50, 75, 90, and 99 percent, there was a 52, 65, 78, and 95 percent chance of passing challenge, respectively.

Summary — Egg allergy appears to affect between 1 and 2 percent of the pediatric population. The majority of cases resolve within childhood or adolescence. As with cow's milk allergy, the rate at which egg-specific IgE levels decrease can be used to assess the likelihood that a child has outgrown the sensitivity.

Peanut and tree nut — Peanut and tree nut allergies are frequently studied together as they coexist in up to 30 to 40 percent of patients [[50-52](#)]. More information is available on the natural history of peanut allergy, and the understanding of it is changing. Although it was initially believed to be a lifelong sensitivity in nearly all cases, subsequent studies have shown that tolerance can develop in approximately 20 to 25 percent of patients. Less is known about tree nut allergy, although a minority of patients appear to lose this sensitivity as well.

Prevalence — The cumulative findings of several studies from the United States and Europe in the late 1990s and early 2000s estimated the prevalence of peanut and tree nut allergies at 0.4 to 1.3 percent in children and 0.5 to 1 percent in the overall population [[50,51,53-56](#)]. As an example, sensitization and clinical reactivity to peanut and tree nuts were studied in a cohort of children on the Isle of Wight [[57](#)]. All children born during a single year were recruited and followed prospectively. By four years of age, 15 of the 1218 participating children (1.2 percent) developed positive skin prick tests to peanut or tree nuts, and approximately half of these (0.5 percent) had allergic reactions upon ingestion. (See "[Peanut, tree nut, and seed allergy: Clinical features](#)".)

Serial studies in the United Kingdom and the United States have suggested that the

prevalence of peanut allergy is increasing over time [51,55,58]. In a random calling telephone survey conducted in the United States, the reported prevalence of peanut allergy in children increased from 0.4 in 1997 to 0.8 percent in 2002 and 1.4 percent in 2008 [51,59]. The estimated overall prevalence in the United States in a national 2005-2006 survey was 1.3 percent, based upon serologic testing [3]. The age of onset also appears to be changing, with the diagnosis being made in progressively younger children [60].

Resolution

- Peanut — Early studies of peanut allergy suggested that it was persistent [61]; however, it is now realized that up to one-quarter of patients become tolerant over time [52,54,62,63].
- One of the first studies to demonstrate resolution evaluated 230 children with a diagnosis of peanut allergy and performed oral challenges in 120 [62]. Those with a negative skin prick test or a history of tolerating peanut were offered a challenge and those with a history of life-threatening reactions were not, so the selection of patients challenged was not randomized. A total of 22 children between the ages of two and nine years had a negative challenge (9.8 percent of the total group). A negative challenge was associated with a smaller-sized skin prick test reaction and fewer allergies to other foods.
- A later study by our group, which demonstrated a rate of resolution of 21.5 percent, evaluated 223 children with the diagnosis of peanut allergy, and included oral challenge in 85 children who had not had a reaction in the past year and who had a (peanut specific-IgE) PN-IgE <20 kUA/L [52]. Children with either a history of a recent reaction or a PN-IgE level >20 kUA/L [33] were considered still allergic and not offered challenge, and an additional 41 children were eligible for challenge but declined. Of the 85 children challenged, 48 (21.5 percent of the total group) passed the challenge and were believed to have outgrown their peanut allergy. Four additional children passed challenges after the study was completed, increasing the rate of resolution to 23.3 percent.
- In a second similar study by our group, 80 peanut allergic children underwent evaluation and challenge (either open or DBPCFC) [54]. All were four years of age or older and had PN-IgE levels ≤ 5 kUA/L at the time of challenge. Upon challenge, 55 percent of patients tolerated peanut overall. Sixty-three percent of children with PN-IgE levels ≤ 2 kUA/L, and 73 percent with negative PN-IgE levels passed. It was notable, however, that eight patients with PN-IgE levels ≤ 0.35 kUA/L failed challenge.

Subsequent dietary behaviors and recurrent reactions were then evaluated by our group using a telephone questionnaire in all patients who passed DBPCFC (ie, tolerated peanut) [52,54]. Of the 64 patients who passed challenges, 97 percent subsequently ate peanut, but most did so infrequently, ie, once a month or less. There were two possible cases of recurrent reactions. (See ['Recurrence'](#) below.)

- Tree nut — Few data exist concerning the resolution of tree nut allergy. In one study that used DBPCFC to confirm the loss of clinical reactivity, the resolution of tree nut allergy was estimated to be at least 9 percent (9 of 101 children) [64]. The rate of resolution increased with lower TN-IgE levels (58, 63, and 75 percent of children with TN-IgE levels <5 kUA/L, <2 kUA/L, and negative TN-IgE levels, respectively).

Factors that did **not** predict the development of tolerance included the severity of the initial reaction and the history of having outgrown other food allergies other than peanut. In contrast, patients who had outgrown peanut allergy were more likely to outgrow tree nut allergy. No child that had reactions to more than two different tree nuts achieved tolerance.

Prognostic factors — The results of serial objective testing appear to be the best indicator of resolution or persistence of nut allergy. An Australian study of 267 children referred to a specialty center and diagnosed with peanut allergy before the age of two years investigated the clinical and laboratory predictors of resolution [63]. A diameter of positive skin prick test wheal ≥ 6 mm or a PN-IgE ≥ 3 kUA/L before the age of two were found to be independent predictors of persistent allergy at age eight years in this population (although these values may not apply to other pediatric populations). Patients whose allergy eventually resolved tended to have positive skin tests of decreasing size between ages one and four years, while patients with persistent allergy typically had increasingly larger positive skin tests. In contrast, this and other studies found that clinical features did not reliably predict persistence; neither the presence of other atopic diseases, age at diagnosis, nor the severity of initial peanut or tree nut reactions predicted subsequent loss of the allergy. (See ['Monitoring the food-allergic child'](#) above.)

Studies evaluating the resolution of both peanut and tree nut allergy also suggest the following:

- Low or undetectable specific IgE levels, as measured by CAP-RAST (or CAP-FEIA), were the best predictors of a negative challenge.
- Challenge was essential to determine the loss of allergy with certainty, as some patients still reacted even when their skin prick tests and/or CAP-RASTs

became completely negative. It has been our estimation that this may occur in as many as 10 percent of patients in such studies.

- Tolerance of peanut does not imply tolerance of tree nuts or seeds. In patients who outgrow peanut allergy, tree nut allergy or seed allergy can persist or subsequently develop for the first time [65]. Potential allergy to these foods must be independently evaluated.

Recurrence — As previously mentioned, recurrent reactions have been reported in patients thought to have outgrown peanut allergy [52,54]. In a third study by our group, recurrent reactions were found in 3 of 36 patients (8 percent) with a clear history of peanut allergy who had previously passed a peanut challenge [66]. An example of a case was a six-year-old girl who had presented at age one year with generalized urticaria and facial angioedema within five minutes of eating a peanut butter cracker. Her PN-IgE level at diagnosis was 2.79 kUA/L, and she had no history of other food allergies. At age 4.5 years her PN-IgE level was 1.1 kUA/L and she passed peanut challenge. She subsequently ate only "may contain peanut" products until approximately 1.8 years after the initial challenge, when she had two bites of Butterfinger ice cream and within 15 minutes developed urticaria, coughing, difficulty breathing, throat tightness, abdominal pain, vomiting, and diarrhea. A repeat PN-IgE level was >100 kUA/L. A SPT was not performed, and a DBPCFC was deferred because of the severity of the reaction and the high PN-IgE level.

In this and several other small series of patients with resolved peanut allergy, it appears that recurrence may be more common among those who continue to avoid peanut or eat it infrequently [52,54,66,67]. In the study previously discussed, each of the three patients with recurrent allergy consumed concentrated peanut products less than once a month [66]. In contrast, none of a group of 23 patients who ate peanut more frequently had recurrent allergy. Thus, infrequent exposure may be a risk factor for resensitization.

Summary — Peanut and tree nut allergy affects at least 0.5 to 1.4 percent of children and 0.5 to 1 percent of the general population, and may be increasing over time. This type of allergy is likely to be a lifelong disorder for most but not all patients. Because a substantial minority (ie, 20 to 25 percent for peanut and 9 percent for tree nut) of patients lose their sensitivity over time, it is appropriate to reevaluate children on a regular basis.

- Patients who have not had reactions in the past one to two years and who have low TN- or PN-IgE levels (≤ 2 kUA/L) should be considered for an oral peanut challenge in a supervised setting. In our clinic, we obtain CAP-FEIA values yearly, and because of safety concerns, only challenge children older

than four years of age. A negative CAP-FEIA is not a guarantee that the allergy is resolved, and challenge is necessary to make this determination.

- Peanut allergy can recur following resolution, although this is unusual. Tree nut allergy has not been studied as well. Infrequent ingestion of peanut may be a risk factor for recurrence, but these data are derived from small numbers of cases.

Wheat allergy — Wheat allergy is also a common childhood food allergy that is usually outgrown by adolescence [[35,68,69](#)]. Concomitant atopic disease and other food allergies are frequently seen [[35](#)].

Wheat allergy related to occupational exposure in adults is discussed separately, as is celiac disease (gluten-sensitive enteropathy). (See "[Respiratory manifestations of food allergy](#)" and "[Clinical manifestations and diagnosis of celiac disease in children](#)" and "[Management of celiac disease in children](#)".)

Prevalence — IgE-mediated wheat allergy has been reported to affect 0.4 to 1 percent of children in the United States (US) and the United Kingdom (UK), where wheat is a staple in the diet [[7,70](#)].

Resolution — In studies of children with food allergy and atopic dermatitis, wheat allergy was outgrown in 25 and 33 percent of children over a one and two year follow-up, respectively [[18,71](#)]. In the general population, wheat allergy resolves in 80 percent of patients by five years of age [[68](#)]. However, tolerance appears to develop more slowly in a highly atopic population followed at a tertiary care center, as is seen in similar populations with cow's milk and hen's egg allergies [[35](#)].

- A retrospective study examined the natural course of IgE-mediated wheat allergy in 103 children followed at a large referral center from 1993 to 2007 [[35](#)]. Oral challenges to wheat were performed in 61 percent during the study period. The median age at which tolerance was acquired was 6.6 years. However, the median age at resolution varied considerably depending upon peak wheat IgE (approximately 2, 4, and 10 years of age for children with peak wheat IgE levels <20, 20 to 50, and >50 kU/L, respectively). Overall, tolerance was achieved by 29, 56, and 70 percent at 4, 8, and 14 years of age, respectively. In children aged two to eight years, the median wheat IgE levels associated with resolved allergy ranged from 21 to 25 kU/L, whereas the median levels associated with persistent allergy ranged from 62 to 70 kU/L. Patients with wheat sensitization (wheat IgE >20 kU/L, but no history of symptomatic exposure) passed challenges at rates similar to the children discussed above who had a history of symptomatic wheat allergy.

Summary — IgE-mediated wheat allergy affects 0.4 to 1 percent of the pediatric population. The majority of cases resolve by adolescence.

The pediatrician treating the general population can expect high rates of resolution, whereas allergy specialists with referred patient populations should anticipate lower resolution rates. We suggest serial oral challenges to wheat at least every two years, regardless of specific IgE level, in the absence of an interval history of symptoms triggered by an exposure (see ['Wheat'](#) above).

Other foods — The natural history of other food allergies is less well studied.

Earlier studies suggested that soy allergy is typically outgrown in the preschool-age years [[14,18,71,72](#)]. However, a subsequent larger retrospective study performed at a tertiary referral clinic found that only about 50 percent of children had outgrown soy allergy by seven years of age [[73](#)]. Soy allergy resolved in 25, 45, and 69 percent by age 4, 6, and 10 years, respectively.

The limited data available suggests that sesame allergy, similar to peanut and tree nut allergies, is more likely to persist [[74-76](#)]. The reported rate of resolution of sesame allergy ranges from 20 to 30 percent.

As mentioned previously, adverse reactions to fruits, vegetables, and other cereal grains are typically very short-lived in children [[17,72,77](#)]. Many of these reactions may represent intolerances or irritant reactions rather than true allergy, and most children will lose their sensitivity to these foods within a period of 6 to 12 months. A minority of children have severe, IgE-mediated allergies to these foods that may persist over time, however.

There are few studies addressing the natural history of seafood (fish and shellfish) allergies. These can develop in childhood, although adult onset is believed to be more common. Seafood allergies are reviewed separately. (See ["Seafood allergies: Fish and shellfish"](#).)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient

education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Beyond the Basics topic (see ["Patient information: Food allergy treatment and avoidance"](#))

SUMMARY AND RECOMMENDATIONS — The peak prevalence of food allergy is approximately 6 to 8 percent at one year of age and then falls progressively. By late childhood, the prevalence is 2 to 4 percent and remains stable thereafter. Food-allergic children are at high risk for developing later allergic rhinitis and asthma. (See ['Prevalence of childhood food allergy'](#) above.)

Resolution of selected food allergies

- Most childhood food allergies are lost over during childhood or adolescence, although certain allergies tend to persist, such as those to fish/shellfish and peanut/tree nut. (See ['Overview of resolution'](#) above.)
- Cow's milk allergy (all types) affects approximately 2.5 percent of children under two years of age. Non-IgE-mediated milk allergy is a transient childhood condition that is almost always outgrown, but must be managed carefully as challenge can be hazardous. IgE-mediated milk allergy may persist into adolescence, although it is usually outgrown by adulthood. (See ['Cow's milk'](#) above.)
- Egg allergy affects 1 to 2 percent of children. The majority of cases resolve by adulthood. (See ['Hen's egg'](#) above.)
- Peanut and tree nut allergies affect about 0.5 to 1.4 percent of children and may be increasing over time. It is likely to be a lifelong disorder for most patients, although 20 to 25 percent outgrow peanut and at least 9 percent outgrow tree nut allergies. Recurrence is rare, although a few cases have been documented. (See ['Peanut and tree nut'](#) above.)

Monitoring and testing — Optimal monitoring of the food-allergic child requires the cooperative input of both the general pediatrician (to assess growth and development) and the allergist (to address ongoing education, proper medication use, and reevaluate allergic status). (See ['Monitoring the food-allergic child'](#) above.)

- Most allergy experts use a combination of historical information from accidental exposures and periodic in vitro and/or skin testing. As an example, a challenge may be offered at a higher specific IgE level if there is a history of a recent accidental exposure without a reaction. Alternatively, a challenge will

not be offered when the specific IgE is below the designated cutoff level if the patient has had a recent exposure that triggered a reaction. (See '[Serial testing](#)' above.)

- Medically supervised food challenge is recommended to confirm that a food allergy has resolved, as in vitro and skin tests can remain positive in patients who achieve clinical tolerance, and conversely, tests can become negative in patients who still react upon ingestion, although the latter situation is uncommon. (See '[Determining if an allergy has resolved](#)' above.)
- For IgE-mediated cow's milk allergy, we repeat milk-specific CAP-FEIA testing yearly and offer challenge when the level is ≤ 2 kUA/L. At this level, the pass rate is approximately 50 percent. (See '[Cow's milk and egg](#)' above.)
- For IgE-mediated egg allergy, we repeat egg-specific CAP-FEIA testing yearly and offer challenge when the specific IgE level is ≤ 2 kUA/L. At this level, the pass rate is approximately 50 percent. (See '[Cow's milk and egg](#)' above.)
- Patients with peanut or tree nut allergy who are over four years of age and have not had reactions in the past one to two years and who have specific CAP-FEIA values ≤ 2 kUA/L should be offered challenge in a supervised setting. At this level the pass rate is approximately 60 percent. (See '[Peanut or tree nut](#)' above.)

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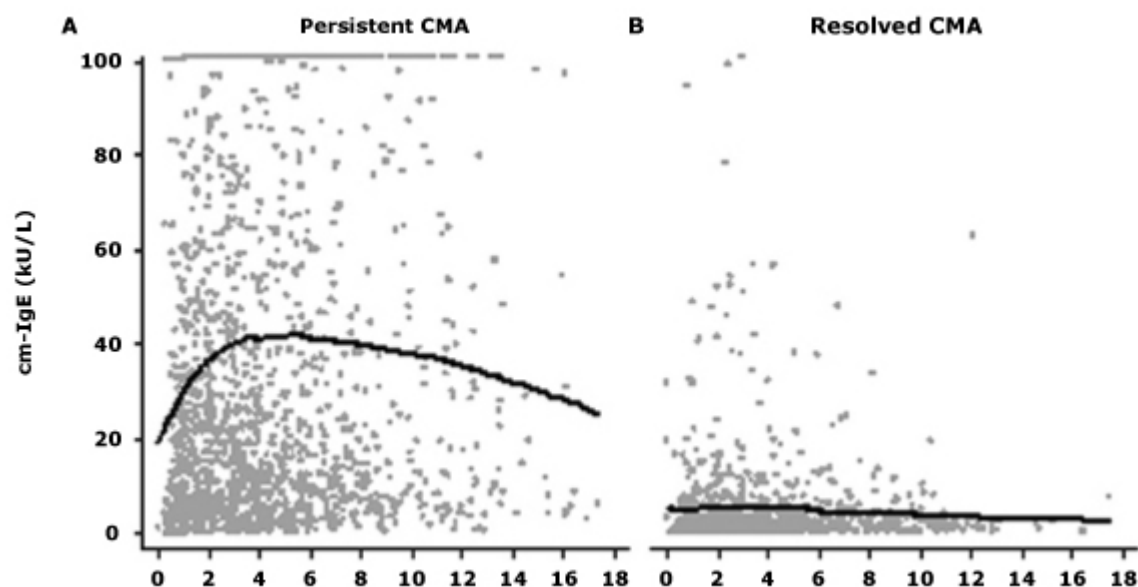
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GRAPHICS

Trend in cm-IgE levels over time by final CMA status



Scatter plots of all cm-IgE levels recorded, by age, to age 18 years ($n = 2498$). Panel A) All values in the group with persistent CMA ($n = 1651$). Panel B) All values in the group with resolved CMA ($n = 847$). Nonparametric smoothed curves show the trend in cm-IgE levels over time. These curves approximate the mean value at any given age.

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